Biomatter 2:3, 149–157; July/August/September 2012; © 2012 Landes Bioscience

Surface modification of implants in long bone

Yvonne Förster,[1,*] Claudia Rentsch,[1] Wolfgang Schneiders,[1] Ricardo Bernhardt,[3] Jan C. Simon,[4] Hartmut Worch[3] and Stefan Rammelt[1,2]

[1]Department of Trauma and Reconstructive Surgery; Center for Translational Bone, Joint and Soft Tissue Research; Dresden University Hospital "Carl Gustav Carus"; Dresden, Germany; [2]DFG Center for Regenerative Therapies Dresden (CRTD); Dresden, Germany; [3]Institute of Material Science; Max Bergmann Center of Biomaterials; Technical University Dresden; Dresden, Germany; [4]Department of Dermatology, Venerology and Allergology; University Leipzig; Leipzig, Germany

Keywords: bone healing, collagen type I, hydroxyapatite, chondroitin sulfate, hyaluronic acid, implants, RGD peptide, titanium

Abbreviations: BIC, bone/implant contact; Coll, collagen type I; CS, chondroitin sulfate; ECM, extracellular matrix; FN, fibronectin; HA, hydroxyapatite; Hya, hyaluronic acid; TRAP, tartrate-resistant acid phosphatase

Coatings of orthopedic implants are investigated to improve the osteoinductive and osteoconductive properties of the implant surfaces and thus to enhance periimplant bone formation. By applying coatings that mimic the extracellular matrix a favorable environment for osteoblasts, osteoclasts and their progenitor cells is provided to promote early and strong fixation of implants. It is known that the early bone ongrowth increases primary implant fixation and reduces the risk of implant failure. This review presents an overview of coating titanium and hydroxyapatite implants with components of the extracellular matrix like collagen type I, chondroitin sulfate and RGD peptide in different small and large animal models. The influence of these components on cells, the inflammation process, new bone formation and bone/implant contact is summarized.

Introduction

Bone healing is a highly complex process which is conventionally divided into three overlapping steps: (1) inflammation, (2) repair and (3) bone remodeling. Each of them is characterized by a specific set of cellular and molecular events.[1-3] Bleeding at the fracture site results in the development of a local hematoma. Inflammatory cells like granulocytes, macrophages, monocytes and lymphocytes infiltrate the hematoma and secrete cytokines and growth factors.[1,2] Chemotactic effects induce further recruitment of inflammatory and mesenchymal cells, stimulation of angiogenesis and extracellular matrix synthesis.[4,5] Over time the hematoma is reorganized in granulation tissue.[6,7] Chondrocytes derived from mesenchymal progenitors and fibroblasts produce osteoid which is subsequently mineralized and form a soft callus between the fragments.[6] In the next step, soft callus is gradually removed and replaced by mineralized bone matrix. The newly formed woven bone is called hard callus, is typically irregular and needs to be remodeled.[7] This repair stage represents the most active period of osteogenesis with high levels of osteoblast activity. In the remodeling phase the woven bone is transformed into lamellar bone with the trabeculae being formed along the pressure trajectories. The most active cells during remodeling are osteoclasts which demineralize the matrix and degrade the organic components by proteinases.[7,8] New bone is laid down in its shape, structure and mechanical strength by osteoblasts.[7]

In summary, the first 1 to 2 weeks, in which inflammation and revascularization occur, seem to be most critical for fracture healing.[6,9] An early formation of granulation tissue could support the differentiation of mesenchymal cells into osteoblasts and thus provide a better requisite for bone remodeling.

Coating of orthopedic implants aims at improved bone/implant contact (BIC), reduction of implant loosening and adverse reactions. Since the host response to surgical implants is mediated by regulatory interactions between the cells and the organic extracellular matrix,[10-12] coating with components of the extracellular bone matrix (ECM) appears attractive to enhance bone healing around metallic and hydroxyapatite (HA) implants. Thereby, the ECM is not only a passive scaffold for cells. Several components of the ECM like collagen type I (Coll), chondroitin sulfate (CS) or RGD peptide containing proteins are able to bind cytokines and growth factors[12,13] and can interact with bone cells via integrins or other specific cell surface receptors[14] thus directly or indirectly influencing migration and cell adhesion as well as proliferation and differentiation of these cells.[15,16]

Osseointegration is influenced by the primary stability (mechanical stability) and secondary stability (biological stability after bone remodeling) of the implant in the bone. Thereby early bone formation and apposition is essential for secondary stability.[17] In this review the promotion of early bone formation by components of the ECM is described.

Collagen Type I on Ti and HA Implants

Collagen type I is the major structural protein in bone. Coating with Coll enhanced in vitro adhesion, migration and differentiation of osteoblasts on Ti disks.[18,19] Furthermore, the osteoconductive properties of Coll in cancellous and cortical bone are well documented.[20-22]

*Correspondence to: Yvonne Förster;
Email: yvonne.foerster@uniklinikum-dresden.de
Submitted: 05/01/12; Revised: 06/24/12; Accepted: 07/20/12
http://dx.doi.org/10.4161/biom.21563

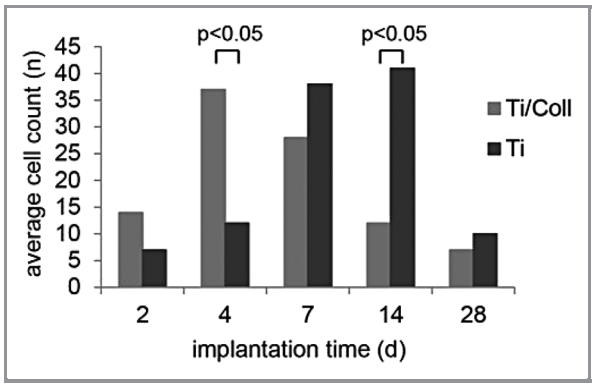

Figure 1. Average cell counts stained against cathepsin D around Ti implants in the rat tibia per lower power field. Cells were counted in three subsequent slices per animal. Statistical significance between Coll-coated and uncoated Ti implants were found as indicated across the bar. The earlier observation of cathepsin D-positive cells at the interface around Coll-coated Ti implants suggest an earlier onset of the bone remodeling process and an earlier decrease of the inflammatory response to the implant compared with uncoated implants.[23]

Coating of Ti pins with Coll showed that the cellular reaction on the implants appeared more intense around the Coll-coated implants in the early stages of bone healing in a rat tibia model compared with uncoated pins.[23,24] At four days after implantation reparative granulation tissue was seen around the Coll-coated implants with 70% of the surface being surrounded by loose granulation tissue. Cathepsin D, osteopontin and osteonectin-positive cells were detected earlier and in higher number around Ti/Coll pins compared with Ti pins (**Fig. 1**). Cathepsin D is an important marker for cells of the monocyte/macrophage lineage and is known to play a role in bone remodeling under both physiological and pathological conditions.[25] Osteopontin and osteonectin are non-collagenous proteins of the ECM. They are produced by osteoblasts and osteocytes and are involved in fracture healing.[26-28] The early appearance of these proteins around Coll-coated Ti pins indicated an earlier onset of the bone remodeling process compared with uncoated Ti pins. After 28 days both coated and uncoated implants were surrounded to a great extent by newly formed lamellar bone with small parts of dense fibrous tissue connecting the distinct bone lamellae. The bone was in close contact with the implants without intervening fibrous tissue (**Fig. 2B and C**). Both the direct BIC and the amount of newly formed bone were greater in Coll-coated implants compared with uncoated implants without reaching statistical significance.[23]

In a sheep tibia model, coating of Ti implants with Coll under loaded conditions (external fixator pins) was investigated (**Fig. 3**).[29] The extraction torque of the external fixation pins was not altered by the Coll-coating after 6 weeks of implantation. However, the apparent new bone formation and significantly increased activity of osteoblasts around the external fixator pins

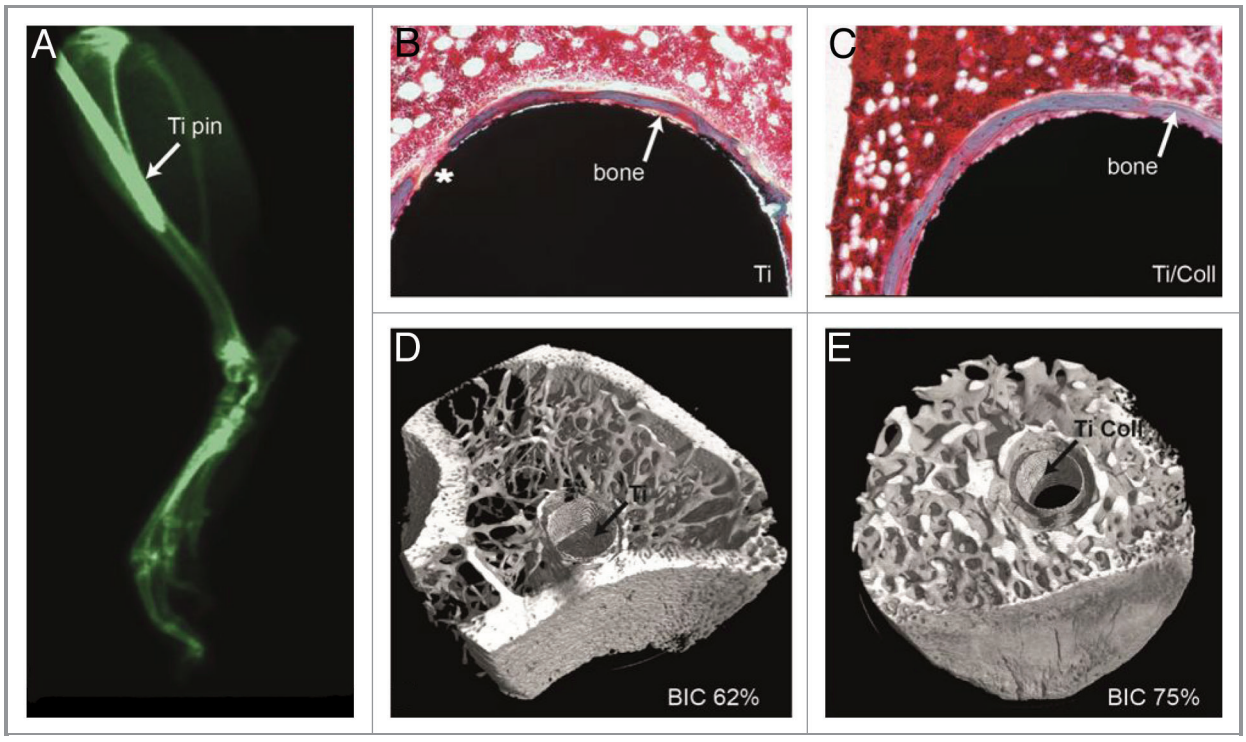

Figure 2. (A) Lateral radiograph of a rat tibia with the Ti implant in situ. (B and C) Undecalcified sections of the bone/implant interface at 28 d after implantation (original magnification × 10) of uncoated (B) and Coll-coated (C) implants. Goldner staining showed slightly more bone contact and thicker bone layer around Coll-coated implants. Around uncoated implants small parts of dense fibrous tissue were seen (*). (D and E) Microcomputed tomographs (SRμCT) of the metaphyseal section of the rat tibia inserted with uncoated (D) and Coll-coated (E) pins. The pins are piled of digitally, mineralized bone appears gray. No image artifacts were observed because of the use of synchrotron radiation.[23] BIC, bone/implant contact.

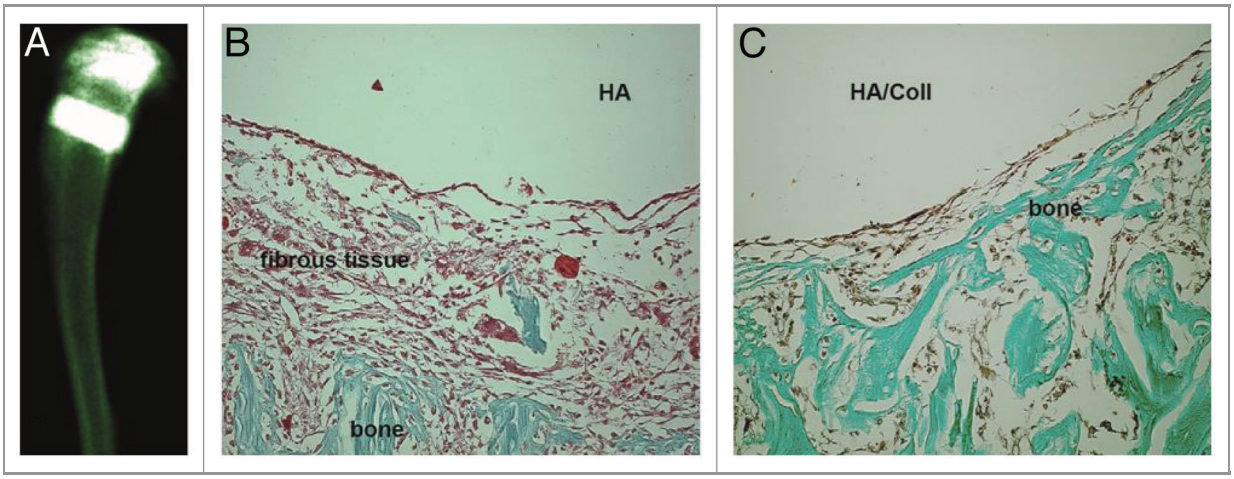

Figure 3. (A) Anteroposterior radiograph of a sheep tibia 6 weeks after surgery with the external fixator and the unloaded implants in the tibial head in situ. (B) Extraction torque of loaded external fixator pins at 6 weeks. The difference between uncoated and coated pins was not statistically significant. (C and D) Goldner stain of unloaded implants did not reveal detectable differences with regard to new bone formation in the cavities of the implant (original magnification × 25). (E and F) New bone formation was seen around all coated external fixater pins in contrast to the uncoated pins (original magnification × 25).[29]

suggested increased bone remodeling around the Coll-coated implants. All data indicated that the faster remodeling by Coll-coating affects primarily the earlier stages of bone healing without altering mechanical stability.[29]

The favorable in vivo results of coating Ti implants with collagen type I were confirmed by other groups. In the dog mandible a significantly increased peri-implant bone formation was found around Coll-coated screws implants after 3 mo as compared with uncoated screws.[30] In the femur condyle of goats the amount of new bone formation was significantly higher in the cavities of cylindric Ti implants after 5 and 12 weeks.[31] In a rabbit femur model Coll-coating of Ti implants enhanced the osseointegration rate after 4 weeks as evaluated by histomorphometry,[32] push-out test[33] and bone microhardness measurements.[34] Coll-coating of commercially available dental implants investigated in the dog mandible resulted in significantly higher BIC after 3 and 8 weeks. In addition, analysis of cells near the bone implant phase showed cellular and molecular profiles of osteoblasts in a more advanced stage of differentiation.[35]

In contrast, Svehla et al.[36] did not observe improved osseointegration of porous Ti cylinders coated with collagen gel implanted into the diaphysis of the sheep tibia. Different animal models, time frames and coating techniques make it difficult to directly compare the different studies.

However, Coll is effective in promoting cellular adhesion and spreading through RGD sequences recognized by integrins.[37] The RGD sequences are able to interact directly with bone cells like osteoblasts, osteoclasts and their precursor cells.[38,39] Salasznyik et al.[40] described strong adhesive interactions of human mesenchymal cells on Coll-coated surfaces in vitro. Furthermore the adhesion to Coll promotes the differentiation of these cells into the osteogenic line. In addition Coll serves as substratum for collagenases and matrix metalloproteinases.[41,42] It is therefore able to enhance bone resorption and bone formation resulting in increased bone remodeling.[23,41]

Hydroxyapatite as bone substitute material is known to be a bioactive and biocompatible material with excellent osteoconductive properties.[43,44] Combination of HA with Coll was found to be particularly suitable for bone replacement[45,46] with good bone cell attachment,[47] biodegradation by macrophages[45] and induction of basic multicellular units in the surrounding tissue.[22,46]

In a rat tibia model the tissue reaction to HA combined with Coll (HA/Coll) was evaluated (**Fig. 4**).[41] The number of cathepsin D-positive cells was significantly increased around HA/Coll implants at day 6 ($p < 0.01$), 14 and 28 ($p < 0.05$). These results suggest that a certain amount of phagocytotic cells, which is required for a successful tissue turnover in the interface region, appeared earlier and prevailed for a longer period around HA/Coll implants. These findings reflect a higher bone remodeling activity around the Coll-modified implants compared with the unmodified HA.[41] Furthermore, the low number of multinucleated cells and markedly decreased macrophage numbers after day 6 indicate that only a short inflammatory reaction took place reflecting the early stages of physiological bone healing. As a result of these early events clusters of newly formed woven bone could be detected around HA/Coll implants at day 6, but not around the implants of pure HA (**Fig. 4**). Histomorphometric analysis showed an averaged BIC of 50.8% around HA/Coll implants and 28.5% around pure HA implants, representing a statistically significant difference ($p < 0.05$).[41]

These findings support the hypothesis from other authors[20,22,46] that the addition of collagen to HA implants can induce ossification processes in the early stage and thus provide better conditions for bone remodeling in the interface region.[41]

Chondroitin Sulfate in Ti and HA Implants

Chondroitin sulfate (CS) is an important glycosaminoglycane found in cartilage as well as in cancellous and cortical bone.[48] It is part of proteoglycans like decorin and aggregan and consists of a

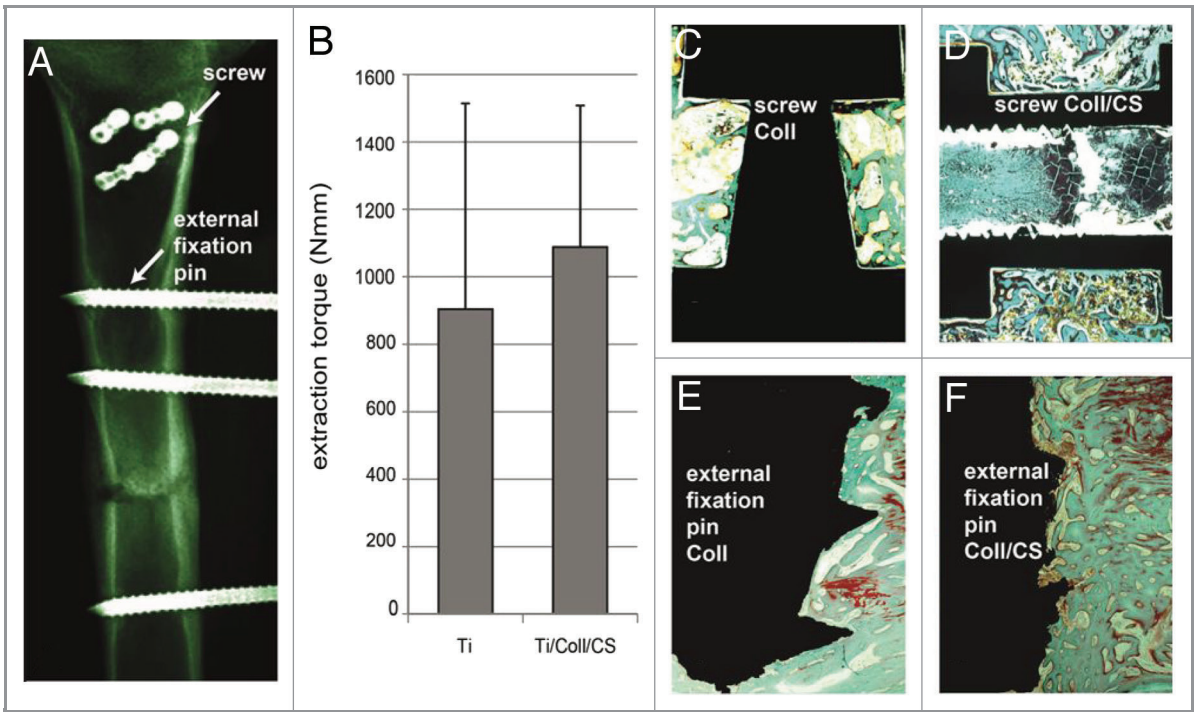

Figure 4. (A) Lateral radiograph of a rat tibia with the inserted cylindrical HA implant (B and C) Goldner stain of the interface region 6 d after implantation of pure HA implants (A) and HA/Coll composites (B). Several islands of newly formed woven bone are seen within the fibrous interface around HA/Coll implants, but not around HA.[41]

repeating disaccharide unit of D-glucuronic acid linked to N-acetylgalactosamine. The galactosamine residues are sulfated in positions 4 or 6. These sulfate groups as well as the carboxyl groups were assumed to interact with mineral structures such as hydroxyapatite in bone.[49,50] Besides Coll, CS appears to be promising as a further addition to biomaterials to enhance bone healing by creating an artificial matrix for osteoblasts. It can mediate the binding of bone-like cells like osteoblasts and osteoclasts to the matrix and capture soluble molecules such as growth factors into the matrix and at cell surfaces.[10]

In vitro studies have shown that the coating of Ti surfaces or textile scaffolds with Coll/CS enhanced mesenchymal cell adhesion, spreading and differentiation.[51-53]

In a standardized rat tibia model Rammelt et al.[24] investigated the effects of Coll/CS-coating on bone remodeling and bone healing. Four days after implantation of the coated Ti pins a reparative granulation tissue was seen around the Coll/CS-coated implants with a high amount of infiltration of mononuclear macrophages displaying immunoreactivity against cathepsin D. At the same time a primitive fibrin network of mainly granulocytes, fibroblasts and few macrophages was observed around uncoated Ti.[24] The number of TRAP-positive osteoclasts at the newly deposited osteoid and woven bone at the implant surface was significantly higher around Coll/CS implants compared with Coll-coated implants or pure Ti ($p < 0.05$). Furthermore, the number of osteopontin-positive cells was significantly increased around the Coll/CS implants at this time point ($p < 0.05$) indicating an early bone remodeling. After 28 d BIC was significantly higher ($p < 0.05$) around Coll/CS-coated Ti pins (89.5%) compared with pure Ti (63.9%) and Coll alone (76.1%).[24]

Further investigations focused on large animal models. In a sheep experiment under loaded conditions the number of osteopontin-positive osteoblasts was significantly increased in the interface around Coll/CS-coated Ti external fixation pins.[29] The extraction torque was slightly higher than that of the uncoated external fixation pins (**Fig. 3**). These data support findings from other groups that have shown that proteoglycans were able to improve cell binding and accelerate differentiation of bone like cells in vivo.[52] Around unloaded Ti screws in the tibia head these effects were not observed, which may be explained by the increased bone remodeling under loaded conditions according to Wolff's law.[54]

Several other animal studies confirmed the advantages of Coll/CS-coating. Stadlinger et al.[5] showed a significantly higher BIC on Coll/CS-coated cylindric Ti implants (40%) compared with Coll-coating (30%) in the mandible of minipigs 6 mo after implantation. The same group studied bone formation using threaded dental Ti implants with different CS content in minipigs.[17] One month after implantation more mature stages of bone formation were reached around the Coll/CS-coated implants in comparison to control independent of the CS amount. The significantly higher BIC after one month was equalized after 2 mo indicating that Coll/CS-coating enhances early bone formation.[17]

The addition of CS to HA/Coll appears attractive in order to further increase the osteoconductive properties of these bone substitute composites. The influence of cylindric CS-modified

HA/Coll implants on the host response was examined in the rat tibia.[55] The HA/Coll implant was not designed to be absorbed by the host tissue. Rather the tissue reaction of the implants could be observed in the interface around the implant. At the early stages of tissue reaction (days 4 and 7) a significantly higher number of cathepsin D-positive and TRAP-positive cells were seen around HA/Coll/CS implants as compared with HA/Coll implants indicating a more rapid tissue reaction and appearance of phagocytotic cells around HA/Coll/CS implants.[56] From the seventh day on, islands of woven bone were observed at the interface around the CS-coated HA/Coll implants, but not around the HA/Coll implants. On day 28 after implantation all implants were surrounded by newly formed lamellar bone with increased amount of BIC and higher amount of newly formed bone around the Coll/CS-coated implants.[55]

These results could be further supported in a large animal model which is more clinically relevant than a small animal model.[57] A critical midshaft defect of 3 cm was created in the tibia and filled with HA/Coll or HA/Coll/CS cement cylinders (**Fig. 5A**). Radiographic investigations of the HA/Coll implants showed no callus reaction until the 12th week whereas an initial callus reaction was seen around the HA/Coll/CS implants. After 3 mo newly formed woven bone was seen directly at the HA implant coated with Coll/CS (**Fig. 5C and D**). Direct bone contact at later stages of bone healing and the total amount of newly formed bone were increased around HA/Coll/CS compared with HA/Coll implants (**Fig. 5B**).

Taken together the results of the small and large animal model indicate additional effects through the addition of CS to Coll than Coll-coating alone. The negative surface charge of CS could be responsible for the observed effects. The negative charged sulfate or carboxyl groups can interact with positively charged amino acid sequences of growth factors thus modulating their activity.[38] This might enhance the immobilization of the growth factors and other cytokines on the implant surface[50] and thus stimulate cell activity around the implants.[55]

In conclusion, CS can mediate the attachment of growth factors and cytokines to the implant surface by direct interaction with them, which should be the subject of further investigations.

RGD on Ti and HA Implants

The RGD peptide sequence (Arg-Gly-Asp) is an ubiquitous adhesive motif.[58] In addition, it is responsible for the interaction of cellular integrin receptors with proteins of the ECM.[59] Numerous in vitro studies have shown that RGD and related peptides are able to enhance adhesion, migration and osteoblast gene expression.[60-62] The RGD sequence is present in several molecules of the ECM like collagen, fibronectin, osteopontin and osteonectin and is thought to play a role in bone formation.

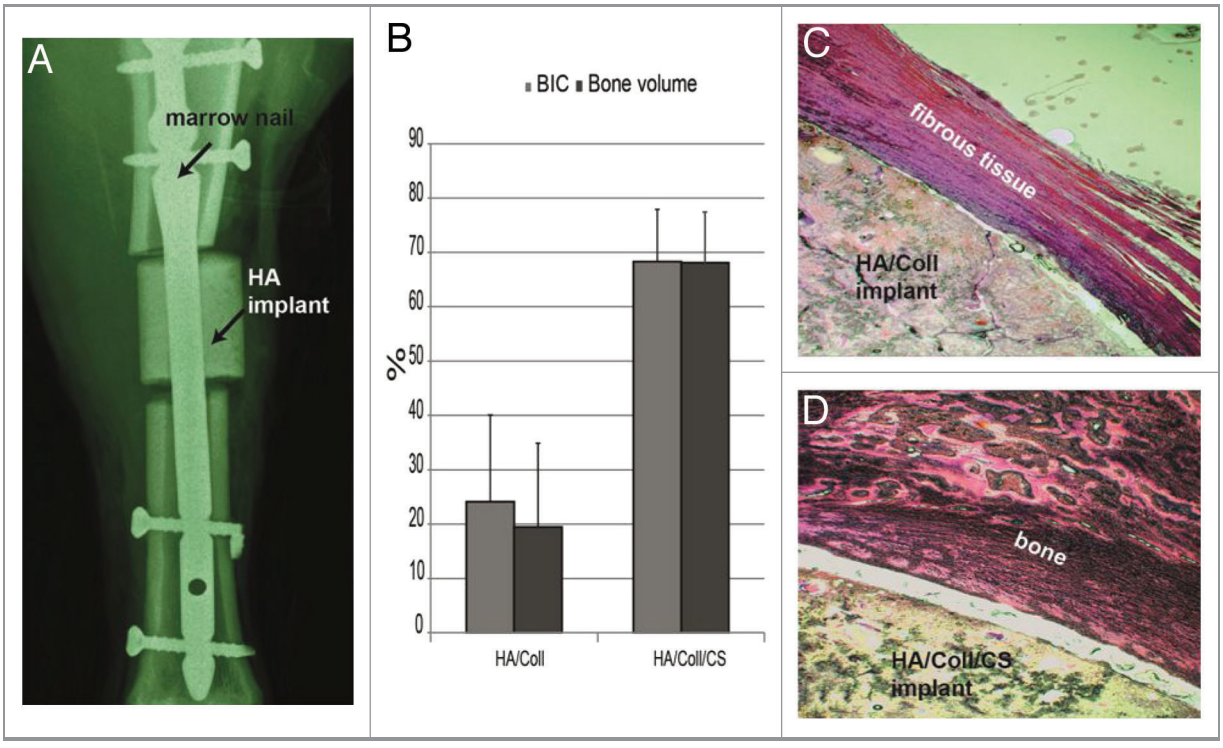

Figure 5. (A) Anteroposterior radiograph of the sheep tibia 12 weeks after surgery with the HA/Coll implant. No callus formation was seen around the implant. (B) Results of histomorphometric measurements after 12 weeks. BIC as well as new bone volume were significantly higher in HA/Coll/CS group compared with the HA/Coll group ($p = 0.002$). (C and D) Morphological changes of the bone-implant interface (Goldner stain, original magnification × 20). Around HA/Coll/CS (D) implants newly formed woven bone is seen directly at the implant surface. There is still remaining fibrous and granulation tissue in the interface around HA/Coll implants (C).[57]

In the rat tibia, histomorphometric analysis of RGD-coated Ti pins showed a significantly enhanced BIC after 4 weeks ($p < 0.05$) as compared with uncoated Ti pins.[24] The appearance of cathepsin D-positive macrophages at day 4 indicated an early bone remodeling activity around the Ti/RGD pins. TRAP-positive osteoclasts appeared 7 d after implantation mostly at the newly deposited osteoid and woven bone at the implant surface. These results indicated a direct activation of macrophages, osteoblasts and osteoclasts in the presence of a RGD sequence at the implant surface.[24] Increased bone formation in the femur of rats could also be detected by Ferris et al.[63] when Ti implants have been coated with RGD.

A more rapid tissue reaction on HA/Coll implants coated with phosphoserine and RGD was detected in a rat tibia model.[64] The early appearance and greater number of TRAP-positive cells suggest an increased bone remodeling around HA/Coll implants additionally coated with phosphoserine and RGD.[64]

A detrimental effect of RGD-coating was noticed by Hennessy et al.[65] They found poor cell adhesion on RGD-coated HA disks and inhibitory effects of RGD on the amount of newly formed bone as well as on the amount of bone directly contacting the implant. Analysis of HA disks after short-term implantation into tibial osteotomies in rats showed that fibronectin (FN), vitronectin and fibrinogen adsorbed within 30 min to the surface. FN, vitronectin and fibrinogen are the most abundant adhesion-promoting proteins in the blood,[66-68] binding integrins through RGD-dependent mechanisms.[69,70] This adsorption may explain the inhibitory effects of FN and vitronectin on cell adhesion. RGD and adsorbed proteins compete for binding to integrin receptors. Binding of high amounts of integrins with RGD rather than the native proteins weakens the integrin signaling resulting in poor cell adhesion and thus osseointegration.[65] No significant differences in bone formation were found with HA/RGD-coated K-wires compared with HA-coating.[71] It was suggested that HA-coating alone has already a beneficial effect on bone formation on the surface.[72-75] This is supported by studies showing that HA-coating is associated with early adhesion of osteoblasts and a direct deposition of bone matrix compared with uncoated implants.[72,76]

On the other hand, Elmengaard et al.[77] found significantly more bone around the RGD-coated implants and improved implant fixation in a loaded as well as unloaded cancellous gap model in the femur of dogs. The same group demonstrated increased bone formation and a reduction in fibrous tissue fixation on the surface of Ti alloy implants coated with RGD in a press-fit model in the tibia of dogs after 4 weeks.[78]

In summary, RGD coating on Ti surfaces seems to enhance new bone formation whereas additional modification of HA implants does not improve BIC and new bone formation.

Further Coatings of Ti and HA Implants

Hyaluronic acid (Hya) is an unbranched and immunologically inert glycosaminoglycan.[79] It is an important component of the extracellular matrix and is involved in regulating cell migration, adhesion and differentiation.[80] Hya with high molecular mass is reported to be osteoinductive.[22,81] In addition, Hya enhances interactions between osteoblasts and osteoclasts in bone remodeling and influences osteoclast progenitor recruitment.[82,83]

Implantation of Ti pins coated with Coll/sulfated Hya in maxillary bone of minipigs did not result in enhanced BIC or bone volume density as compared with uncoated Ti implants.[84] It is known that sulfation plays an important role in growth factor-glycosaminoglycan interactions. Heparin, another glycosaminoglycan, can increase bone morphogenetic protein induced osteoblast differentiation, but desulfated heparin-derivates lose these properties.[85]

In a 4-week rabbit femur model, Hya coating increased BIC, bone ingrowth, implant mechanical fixation and bone maturation suggesting enhanced or faster bone remodeling.[86] Thereby the influence of Hya on osseointegration was more evident in trabecular than in cortical bone. In contrast, Hya-coated HA implants did not increase bone ingrowth in a sheep model.[87]

Fibronectin, a major component of cell adhesive proteins, is known to play a role in facilitating cell attachment, spreading and differentiation.[88-90] Differentiation of osteoblasts was enhanced on Ti surfaces coated with a recombinant fragment of FN containing the central cell binding domain.[91]

In a rat cortical bone model BIC, mechanical fixation, and functional osseointegration were significantly improved compared with uncoated Ti implants and implants coated with FN from human plasma.[91] However, plasma FN coating also showed significantly higher mineralization compared with uncoated implants.[91] In a cylindrical bone defect in the femur of mice acrylic rods coated with Ti and Ti/FN were investigated. The coating with FN from mouse plasma induced earlier osseointegration. BIC was significantly higher at day 5 after implantation around the Ti/FN rods.[92]

Attachment and proliferation of osteoblasts was significantly increased on HA disks pretreated with FN together with fetal calf serum.[93]

Summary and Outlook

Coating of titanium or hydroxyapatite implants with organic components of the extracellular matrix offers great potential to improve new bone formation and enhance bone/implant contact which in turn will improve healing time and implant stability. Nevertheless the sometimes conflicting results necessitate further investigations to individually tailor the ideal implant modifications. The increasing knowledge about the role of the ECM for recruitment, proliferation, and differentiation of cells and regeneration of tissue will eventually deal to the creating of an artificial ECM on the implant that could allow a defined adjustment of the required properties to support the healing process.

A potential strategy could be the sulfation of glycosaminoglycanes to specifically address the functionalities of these ECM components.[94] To further elucidate the basic mechanisms of the cell-matrix interactions during the early stages of bone healing in order to specifically address them with novel implant modifications, our group has used microdialysis on a bone defect model to detect the time-dependent course of the key mediators and cytokines during that process.[95,96]

Acknowledgments

The authors would like to acknowledge the German Research Council (DFG SFB-TR67) and the CRTD.

References

1. Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. J Cell Biochem 2003; a88:873-84; PMID:12616527; http://dx.doi.org/10.1002/jcb.10435
2. Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res 1998(Suppl):S7-21; PMID:9917622; http://dx.doi.org/10.1097/00003086-199810001-00003
3. Bolander ME. Regulation of fracture repair by growth factors. Proc Soc Exp Biol Med 1992; 200:165-70; PMID:1374563
4. Gerstenfeld LC, Cho TJ, Kon T, Aizawa T, Tsay A, Fitch J, et al. Impaired fracture healing in the absence of TNF-alpha signaling: the role of TNF-alpha in endochondral cartilage resorption. J Bone Miner Res 2003; b18:1584-92; PMID:12968667; http://dx.doi.org/10.1359/jbmr.2003.18.9.1584
5. Kon T, Cho TJ, Aizawa T, Yamazaki M, Nooh N, Graves D, et al. Expression of osteoprotegerin, receptor activator of NF-kappaB ligand (osteoprotegerin ligand) and related proinflammatory cytokines during fracture healing. J Bone Miner Res 2001; 16:1004-14; PMID:11393777; http://dx.doi.org/10.1359/jbmr.2001.16.6.1004
6. Kalfas IH. Principles of bone healing. Neurosurg Focus 2001; 10:E1; PMID:16732625; http://dx.doi.org/10.3171/foc.2001.10.4.2
7. Schindeler A, McDonald MM, Bokko P, Little DG. Bone remodeling during fracture repair: The cellular picture. Semin Cell Dev Biol 2008; 19:459-66; PMID:18692584; http://dx.doi.org/10.1016/j.semcdb.2008.07.004
8. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000; 289:1504-8; PMID:10968780; http://dx.doi.org/10.1126/science.289.5484.1504
9. Bastian O, Pillay J, Alblas J, Leenen L, Koenderman L, Blokhuis T. Systemic inflammation and fracture healing. J Leukoc Biol 2011; 89:669-73; PMID:21208896; http://dx.doi.org/10.1189/jlb.0810446
10. Ruoslahti E, Yamaguchi Y. Proteoglycans as modulators of growth factor activities. Cell 1991; 64:867-9; PMID:2001586; http://dx.doi.org/10.1016/0092-8674(91)90308-L
11. Puleo DA, Nanci A. Understanding and controlling the bone-implant interface. Biomaterials 1999; 20:2311-21; PMID:10614937; http://dx.doi.org/10.1016/S0142-9612(99)00160-X
12. Schönherr E, Hausser HJ. Extracellular matrix and cytokines: a functional unit. Dev Immunol 2000; 7:89-101; PMID:11097204; http://dx.doi.org/10.1155/2000/31748
13. Taylor KR, Gallo RL. Glycosaminoglycans and their proteoglycans: host-associated molecular patterns for initiation and modulation of inflammation. FASEB J 2006; 20:9-22; PMID:16394262; http://dx.doi.org/10.1096/fj.05-4682rev
14. Lee JW, Juliano R. Mitogenic signal transduction by integrin- and growth factor receptor-mediated pathways. Mol Cells 2004; 17:188-202; PMID:15179030
15. Ruoslahti E. Proteoglycans in cell regulation. J Biol Chem 1989; 264:13369-72; PMID:2668264
16. Streuli C. Extracellular matrix remodelling and cellular differentiation. Curr Opin Cell Biol 1999; 11:634-40; PMID:10508658; http://dx.doi.org/10.1016/S0955-0674(99)00026-5
17. Stadlinger B, Bierbaum S, Grimmer S, Schulz MC, Kuhlisch E, Scharnweber D, et al. Increased bone formation around coated implants. J Clin Periodontol 2009; 36:698-704; PMID:19531092; http://dx.doi.org/10.1111/j.1600-051X.2009.01435.x
18. Geissler U, Hempel U, Wolf C, Scharnweber D, Worch H, Wenzel K. Collagen type I-coating of Ti6Al4V promotes adhesion of osteoblasts. J Biomed Mater Res 2000; 51:752-60; PMID:10880125; http://dx.doi.org/10.1002/1097-4636(20000915)51:4<752::AID-JBM25>3.0.CO;2-7
19. Roehlecke C, Witt M, Kasper M, Schulze E, Wolf C, Hofer A, et al. Synergistic effect of titanium alloy and collagen type I on cell adhesion, proliferation and differentiation of osteoblast-like cells. Cells Tissues Organs 2001; 168:178-87; PMID:11173803; http://dx.doi.org/10.1159/000047833
20. Johnson KD, Frierson KE, Keller TS, Cook C, Scheinberg R, Zerwekh J, et al. Porous ceramics as bone graft substitutes in long bone defects: a biomechanical, histological, and radiographic analysis. J Orthop Res 1996; 14:351-69; PMID:8676247; http://dx.doi.org/10.1002/jor.1100140304
21. Caiazza S, Colangelo P, Bedini R, Formisano G, De Angelis G, Barrucci S. Evaluation of guided bone regeneration in rabbit femur using collagen membranes. Implant Dent 2000; 9:219-25; PMID:11307408; http://dx.doi.org/10.1097/00008505-200009030-00007
22. Itoh S, Kikuchi M, Takakuda K, Koyama Y, Matsumoto HN, Ichinose S, et al. The biocompatibility and osteoconductive activity of a novel hydroxyapatite/collagen composite biomaterial, and its function as a carrier of rhBMP-2. J Biomed Mater Res 2001; 54:445-53; PMID:11189053; http://dx.doi.org/10.1002/1097-4636(20010305)54:3<445::AID-JBM190>3.0.CO;2-9
23. Rammelt S, Schulze E, Bernhardt R, Hanisch U, Scharnweber D, Worch H, et al. Coating of titanium implants with type-I collagen. J Orthop Res 2004; a22:1025-34; PMID:15304275; http://dx.doi.org/10.1016/j.orthres.2004.02.011
24. Rammelt S, Illert T, Bierbaum S, Scharnweber D, Zwipp H, Schneiders W. Coating of titanium implants with collagen, RGD peptide and chondroitin sulfate. Biomaterials 2006; 27:5561-71; PMID:16879866; http://dx.doi.org/10.1016/j.biomaterials.2006.06.034
25. Nakase T, Kaneko M, Tomita T, Myoui A, Ariga K, Sugamoto K, et al. Immunohistochemical detection of cathepsin D, K, and L in the process of endochondral ossification in the human. Histochem Cell Biol 2000; 114:21-7; PMID:10959819
26. Sato M, Yasui N, Nakase T, Kawahata H, Sugimoto M, Hirota S, et al. Expression of bone matrix proteins mRNA during distraction osteogenesis. J Bone Miner Res 1998; 13:1221-31; PMID:9718189; http://dx.doi.org/10.1359/jbmr.1998.13.8.1221
27. Schulze E, Witt M, Kasper M, Löwik CW, Funk RH. Immunohistochemical investigations on the differentiation marker protein E11 in rat calvaria, calvaria cell culture and the osteoblastic cell line ROS 17/2.8. Histochem Cell Biol 1999; 111:61-9; PMID:9930885; http://dx.doi.org/10.1007/s004180050334
28. Nakase T, Sugimoto M, Sato M, Kaneko M, Tomita T, Sugamoto K, et al. Switch of osteonectin and osteopontin mRNA expression in the process of cartilage-to-bone transition during fracture repair. Acta Histochem 1998; 100:287-95; PMID:9717566; http://dx.doi.org/10.1016/S0065-1281(98)80015-9
29. Rammelt S, Heck C, Bernhardt R, Bierbaum S, Scharnweber D, Goebbels J, et al. In vivo effects of coating loaded and unloaded Ti implants with collagen, chondroitin sulfate, and hydroxyapatite in the sheep tibia. J Orthop Res 2007; 25:1052-61; PMID:17457829; http://dx.doi.org/10.1002/jor.20403
30. Schliephake H, Scharnweber D, Dard M, Sewing A, Aref A, Roessler S. Functionalization of dental implant surfaces using adhesion molecules. J Biomed Mater Res B Appl Biomater 2005; 73:88-96; PMID:15786448; http://dx.doi.org/10.1002/jbm.b.30183
31. Bernhardt R, van den Dolder J, Bierbaum S, Beutner R, Scharnweber D, Jansen J, et al. Osteoconductive modifications of Ti-implants in a goat defect model: characterization of bone growth with SR muCT and histology[Erratum in: Biomaterials 2006;27:670]. Biomaterials 2005; 26:3009-19; PMID:15603796; http://dx.doi.org/10.1016/j.biomaterials.2004.08.030
32. Morra M, Cassinelli C, Cascardo G, Cahalan P, Cahalan L, Fini M, et al. Surface engineering of titanium by collagen immobilization. Surface characterization and in vitro and in vivo studies. Biomaterials 2003; 24:4639-54; PMID:12951007; http://dx.doi.org/10.1016/S0142-9612(03)00360-0
33. Morra M, Cassinelli C, Fini M, Giardino R. Enhanced osseointegration by biochemical surface modification: Covalent linking of collagen I to intervertebral metal disk surface. Eur Cell Mater 2005; 10(Suppl. 3):6.
34. Morra M, Cassinelli C, Meda L, Fini M, Giavaresi G, Giardino R. Surface analysis and effects on interfacial bone microhardness of collagen-coated titanium implants: a rabbit model. Int J Oral Maxillofac Implants 2005; 20:23-30; PMID:15747670
35. Sverzut AT, Crippa GE, Morra M, de Oliveira PT, Beloti MM, Rosa AL. Effects of type I collagen coating on titanium osseointegration: histomorphometric, cellular and molecular analyses[Epub ahead of print]. Biomed Mater 2012; 7:035007; PMID:22406648; http://dx.doi.org/10.1088/1748-6041/7/3/035007
36. Svehla M, Morberg P, Bruce W, Walsh WR. No effect of a type I collagen gel coating in uncemented implant fixation. J Biomed Mater Res B Appl Biomater 2005; 74:423-8; PMID:15889431; http://dx.doi.org/10.1002/jbm.b.30256
37. Ruoslahti E, Pierschbacher MD. New perspectives in cell adhesion: RGD and integrins. Science 1987; 238:491-7; PMID:2821619; http://dx.doi.org/10.1126/science.2821619
38. Andres JL, DeFalcis D, Noda M, Massagué J. Binding of two growth factor families to separate domains of the proteoglycan betaglycan. J Biol Chem 1992; 267:5927-30; PMID:1556106
39. Brighton CT, Albelda SM. Identification of integrin cell-substratum adhesion receptors on cultured rat bone cells. J Orthop Res 1992; 10:766-73; PMID:1403289; http://dx.doi.org/10.1002/jor.1100100604
40. Salasznyk RM, Williams WA, Boskey A, Batorsky A, Plopper GE. Adhesion to Vitronectin and Collagen I Promotes Osteogenic Differentiation of Human Mesenchymal Stem Cells. J Biomed Biotechnol 2004; 2004:24-34; PMID:15123885; http://dx.doi.org/10.1155/S1110724304306017
41. Rammelt S, Schulze E, Witt M, Petsch E, Biewener A, Pompe W, et al. Collagen type I increases bone remodelling around hydroxyapatite implants in the rat tibia. Cells Tissues Organs 2004; b178:146-57; PMID:15655332; http://dx.doi.org/10.1159/000082245

42. Bradt JH, Mertig M, Teresiak A, Pompe W. Biomimetic mineralization of collagen by combined fibril assembly and calcium phosphate formation. Chem Mater 1999; 11:2694-701; http://dx.doi.org/10.1021/cm991002p
43. Layman DL, Ardoin RC. An in vitro system for studying osteointegration of dental implants utilizing cells grown on dense hydroxyapatite disks. J Biomed Mater Res 1998; 40:282-90; PMID:9549623; http://dx.doi.org/10.1002/(SICI)1097-4636(199805)40:2<282::AID-JBM13>3.0.CO;2-O
44. Hamadouche M, Sedel L. Ceramics in orthopaedics. J Bone Joint Surg Br 2000; 82:1095-9; PMID:11132264; http://dx.doi.org/10.1302/0301-620X.82B8.11744
45. Cui FZ, Du C, Su XW, Zhu XD, Zhao NM. Biodegradation of a nano-hydroxyapatite/collagen composite by peritoneal monocyte-macrophages. Cells Mater 1996; 6:31-44.
46. Du C, Cui FZ, Feng QL, Zhu XD, de Groot K. Tissue response to nano-hydroxyapatite/collagen composite implants in marrow cavity. J Biomed Mater Res 1998; 42:540-8; PMID:9827677; http://dx.doi.org/10.1002/(SICI)1097-4636(19981215)42:4<540::AID-JBM9>3.0.CO;2-2
47. Du C, Cui FZ, Zhu XD, de Groot K. Three-dimensional nano-HAp/collagen matrix loading with osteogenic cells in organ culture. J Biomed Mater Res 1999; 44:407-15; PMID:10397944; http://dx.doi.org/10.1002/(SICI)1097-4636(19990315)44:4<407::AID-JBM6>3.0.CO;2-T
48. Sato S, Rahemtulla F, Prince CW, Tomana M, Butler WT. Proteoglycans of adult bovine compact bone. Connect Tissue Res 1985; 14:65-75; PMID:2934215; http://dx.doi.org/10.3109/03008208509089844
49. Bali JP, Cousse H, Neuzil E. Biochemical basis of the pharmacologic action of chondroitin sulfates on the osteoarticular system. Semin Arthritis Rheum 2001; 31:58-68; PMID:11503140; http://dx.doi.org/10.1053/sarh.2000.24874
50. Rhee SH, Tanaka J. Self-assembly phenomenon of hydroxyapatite nanocrystals on chondroitin sulfate. J Mater Sci Mater Med 2002; 13:597-600; PMID:15348590; http://dx.doi.org/10.1023/A:1015135112302
51. Bierbaum S, Douglas T, Hanke T, Scharnweber D, Tippelt S, Monsees TK, et al. Collageneous matrix coatings on titanium implants modified with decorin and chondroitin sulfate: characterization and influence on osteoblastic cells. J Biomed Mater Res A 2006; 77:551-62; PMID:16498599; http://dx.doi.org/10.1002/jbm.a.30572
52. Wollenweber M, Domaschke H, Hanke T, Boxberger S, Schmack G, Gliesche K, et al. Mimicked bioartificial matrix containing chondroitin sulphate on a textile scaffold of poly(3-hydroxybutyrate) alters the differentiation of adult human mesenchymal stem cells. Tissue Eng 2006; 12:345-59; PMID:16548693; http://dx.doi.org/10.1089/ten.2006.12.345
53. Rentsch B, Hofmann A, Breier A, Rentsch C, Scharnweber D. Embroidered and surface modified polycaprolactone-co-lactide scaffolds as bone substitute: in vitro characterization. Ann Biomed Eng 2009; 37:2118-28; PMID:19626441; http://dx.doi.org/10.1007/s10439-009-9731-0
54. Frost HM. Osteogenesis imperfecta. The set point proposal (a possible causative mechanism). Clin Orthop Relat Res 1987; 216:280-97; PMID:3545603
55. Schneiders W, Reinstorf A, Ruhnow M, Rehberg S, Heineck J, Hinterseher I, et al. Effect of chondroitin sulphate on material properties and bone remodelling around hydroxyapatite/collagen composites. J Biomed Mater Res A 2008; 85:638-45; PMID:17806118; http://dx.doi.org/10.1002/jbm.a.31611
56. Rammelt S, Neumann M, Hanisch U, Reinstorf A, Pompe W, Zwipp H, et al. Osteocalcin enhances bone remodeling around hydroxyapatite/collagen composites. J Biomed Mater Res A 2005; 73:284-94; PMID:15800855; http://dx.doi.org/10.1002/jbm.a.30263
57. Schneiders W, Reinstorf A, Biewener A, Serra A, Grass R, Kinscher M, et al. In vivo effects of modification of hydroxyapatite/collagen composites with and without chondroitin sulphate on bone remodeling in the sheep tibia. J Orthop Res 2009; 27:15-21; PMID:18634066; http://dx.doi.org/10.1002/jor.20719
58. Pierschbacher MD, Ruoslahti E. Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule. Nature 1984; 309:30-3; PMID:6325925; http://dx.doi.org/10.1038/309030a0
59. Horton MA. Interactions of connective tissue cells with the extracellular matrix. Bone 1995; 17(Suppl):51S-3S; PMID:8579898; http://dx.doi.org/10.1016/8756-3282(95)00177-F
60. Dee KC, Anderson TT, Bizios R. Osteoblast population migration characteristics on substrates modified with immobilized adhesive peptides. Biomaterials 1999; 20:221-7; PMID:10030598; http://dx.doi.org/10.1016/S0142-9612(98)00161-6
61. Rezania A, Thomas CH, Branger AB, Waters CM, Healy KE. The detachment strength and morphology of bone cells contacting materials modified with a peptide sequence found within bone sialoprotein. J Biomed Mater Res 1997; 37:9-19; PMID:9335344; http://dx.doi.org/10.1002/(SICI)1097-4636(199710)37:1<9::AID-JBM2>3.0.CO;2-W
62. Zreiqat H, Akin FA, Howlett CR, Markovic B, Haynes D, Lateef S, et al. Differentiation of human bone-derived cells grown on GRGDSP-peptide bound titanium surfaces. J Biomed Mater Res A 2003; 64:105-13; PMID:12483702; http://dx.doi.org/10.1002/jbm.a.10376
63. Ferris DM, Moodie GD, Dimond PM, Gioranni CW, Ehrlich MG, Valentini RF. RGD-coated titanium implants stimulate increased bone formation in vivo. Biomaterials 1999; 20:2323-31; PMID:10614938; http://dx.doi.org/10.1016/S0142-9612(99)00161-1
64. Schneiders W, Reinstorf A, Pompe W, Grass R, Biewener A, Holch M, et al. Effect of modification of hydroxyapatite/collagen composites with sodium citrate, phosphoserine, phosphoserine/RGD-peptide and calcium carbonate on bone remodelling. Bone 2007; 40:1048-59; PMID:17223400; http://dx.doi.org/10.1016/j.bone.2006.11.019
65. Hennessy KM, Clem WC, Phipps MC, Sawyer AA, Shaikh FM, Bellis SL. The effect of RGD peptides on osseointegration of hydroxyapatite biomaterials. Biomaterials 2008; 29:3075-83; PMID:18440064; http://dx.doi.org/10.1016/j.biomaterials.2008.04.014
66. Preissner KT. Structure and biological role of vitronectin. Annu Rev Cell Biol 1991; 7:275-310; PMID:1725600; http://dx.doi.org/10.1146/annurev.cb.07.110191.001423
67. Dahlbäck B. Blood coagulation. Lancet 2000; 355:1627-32; PMID:10821379; http://dx.doi.org/10.1016/S0140-6736(00)02225-X
68. Mosher DF. Physiology of fibronectin. Annu Rev Med 1984; 35:561-75; PMID:6326663; http://dx.doi.org/10.1146/annurev.me.35.020184.003021
69. Wilson CJ, Clegg RE, Leavesley DI, Pearcy MJ. Mediation of biomaterial-cell interactions by adsorbed proteins: a review. Tissue Eng 2005; 11:1-18; PMID:15738657; http://dx.doi.org/10.1089/ten.2005.11.1
70. Ruoslahti E. The RGD story: a personal account. Matrix Biol 2003; 22:459-65; PMID:14667838; http://dx.doi.org/10.1016/S0945-053X(03)00083-0
71. Bitschnau A, Alt V, Böhner F, Heerich KE, Margesin E, Hartmann S, et al. Comparison of new bone formation, implant integration, and biocompatibility between RGD-hydroxyapatite and pure hydroxyapatite coating for cementless joint prostheses–an experimental study in rabbits. J Biomed Mater Res B Appl Biomater 2009; 88:66-74; PMID:18615683; http://dx.doi.org/10.1002/jbm.b.31150
72. Pazzaglia UE, Brossa F, Zatti G, Chiesa R, Andrini L. The relevance of hydroxyapatite and spongious titanium coatings in fixation of cementless stems. An experimental comparative study in rat femur employing histological and microangiographic techniques. Arch Orthop Trauma Surg 1998; 117:279-85; PMID:9581262; http://dx.doi.org/10.1007/s004020050247
73. Stephenson PK, Freeman MA, Revell PA, Germain J, Tuke M, Pirie CJ. The effect of hydroxyapatite coating on ingrowth of bone into cavities in an implant. J Arthroplasty 1991; 6:51-8; PMID:1849985; http://dx.doi.org/10.1016/S0883-5403(06)80157-9
74. Søballe K, Hansen ES, Brockstedt-Rasmussen H, Pedersen CM, Bünger C. Hydroxyapatite coating enhances fixation of porous coated implants. A comparison in dogs between press fit and noninterference fit. Acta Orthop Scand 1990; 61:299-306; PMID:2402977; http://dx.doi.org/10.3109/17453679008993521
75. Søballe K, Hansen ES, Brockstedt-Rasmussen H, Hjortdal VE, Juhl GI, Pedersen CM, et al. Gap healing enhanced by hydroxyapatite coating in dogs. Clin Orthop Relat Res 1991; 272:300-7; PMID:1657476
76. Roessler S, Born R, Scharnweber D, Worch H, Sewing A, Dard M. Biomimetic coatings functionalized with adhesion peptides for dental implants. J Mater Sci Mater Med 2001; 12:871-7; PMID:15348332; http://dx.doi.org/10.1023/A:1012807621414
77. Elmengaard B, Bechtold JE, Søballe K. In vivo effects of RGD-coated titanium implants inserted in two bone-gap models. J Biomed Mater Res A 2005; a75:249-55; PMID:16106438; http://dx.doi.org/10.1002/jbm.a.30301
78. Elmengaard B, Bechtold JE, Søballe K. In vivo study of the effect of RGD treatment on bone ongrowth on press-fit titanium alloy implants. Biomaterials 2005; b26:3521-6; PMID:15621242; http://dx.doi.org/10.1016/j.biomaterials.2004.09.039
79. Bastow ER, Byers S, Golub SB, Clarkin CE, Pitsillides AA, Fosang AJ. Hyaluronan synthesis and degradation in cartilage and bone. Cell Mol Life Sci 2008; 65:395-413; PMID:17965830; http://dx.doi.org/10.1007/s00018-007-7360-z
80. Huang L, Cheng YY, Koo PL, Lee KM, Qin L, Cheng JC, et al. The effect of hyaluronan on osteoblast proliferation and differentiation in rat calvarial-derived cell cultures. J Biomed Mater Res A 2003; 66:880-4; PMID:12926041; http://dx.doi.org/10.1002/jbm.a.10535
81. Sasaki T, Watanabe C. Stimulation of osteoinduction in bone wound healing by high-molecular hyaluronic acid. Bone 1995; 16:9-15; PMID:7742090
82. Wong GL. Paracrine interactions in bone-secreted products of osteoblasts permit osteoclasts to respond to parathyroid hormone. J Biol Chem 1984; 259:4019-22; PMID:6323452
83. Cao JJ, Singleton PA, Majumdar S, Boudignon B, Burghardt A, Kurimoto P, et al. Hyaluronan increases RANKL expression in bone marrow stromal cells through CD44. J Bone Miner Res 2005; 20:30-40; PMID:15619667; http://dx.doi.org/10.1359/JBMR.041014
84. Stadlinger B, Hintze V, Bierbaum S, Möller S, Schulz MC, Mai R, et al. Biological functionalization of dental implants with collagen and glycosaminoglycans-A comparative study. J Biomed Mater Res B Appl Biomater 2011; 100B:331-41; PMID:22102613; http://dx.doi.org/10.1002/jbm.b.31953
85. Takada T, Katagiri T, Ifuku M, Morimura N, Kobayashi M, Hasegawa K, et al. Sulfated polysaccharides enhance the biological activities of bone morphogenetic proteins. J Biol Chem 2003; 278:43229-35; PMID:12912996; http://dx.doi.org/10.1074/jbc.M300937200

86. Morra M, Cassinelli C, Cascardo G, Fini M, Giavaresi G, Giardino R. Covalently-linked hyaluronan promotes bone formation around Ti implants in a rabbit model. J Orthop Res 2009; 27:657-63; PMID:18991337; http://dx.doi.org/10.1002/jor.20797
87. Aebli N, Stich H, Schawalder P, Theis JC, Krebs J. Effects of bone morphogenetic protein-2 and hyaluronic acid on the osseointegration of hydroxyapatite-coated implants: an experimental study in sheep. J Biomed Mater Res A 2005; 73:295-302; PMID:15834931; http://dx.doi.org/10.1002/jbm.a.30299
88. van den Dolder J, Bancroft GN, Sikavitsas VI, Spauwen PH, Mikos AG, Jansen JA. Effect of fibronectin- and collagen I-coated titanium fiber mesh on proliferation and differentiation of osteogenic cells. Tissue Eng 2003; 9:505-15; PMID:12857418; http://dx.doi.org/10.1089/107632703322066688
89. Grzesik WJ, Robey PG. Bone matrix RGD glycoproteins: immunolocalization and interaction with human primary osteoblastic bone cells in vitro. J Bone Miner Res 1994; 9:487-96; PMID:7518179; http://dx.doi.org/10.1002/jbmr.5650090408
90. Grzesik WJ, Ivanov B, Robey FA, Southerland J, Yamauchi M. Synthetic integrin-binding peptides promote adhesion and proliferation of human periodontal ligament cells in vitro. J Dent Res 1998; 77:1606-12; PMID:9719034; http://dx.doi.org/10.1177/00220345980770080801
91. Petrie TA, Reyes CD, Burns KL, García AJ. Simple application of fibronectin-mimetic coating enhances osseointegration of titanium implants. J Cell Mol Med 2009; 13(8B):2602-12; PMID:18752639; http://dx.doi.org/10.1111/j.1582-4934.2008.00476.x
92. Jimbo R, Sawase T, Shibata Y, Hirata K, Hishikawa Y, Tanaka Y, et al. Enhanced osseointegration by the chemotactic activity of plasma fibronectin for cellular fibronectin positive cells. Biomaterials 2007; 28:3469-77; PMID:17512051; http://dx.doi.org/10.1016/j.biomaterials.2007.04.029
93. Schönmeyr BH, Wong AK, Li S, Gewalli F, Cordiero PG, Mehrara BJ. Treatment of hydroxyapatite scaffolds with fibronectin and fetal calf serum increases osteoblast adhesion and proliferation in vitro. Plast Reconstr Surg 2008; 121:751-62; PMID:18317125; http://dx.doi.org/10.1097/01.prs.0000299312.02227.81
94. Franz S, Rammelt S, Scharnweber D, Simon JC. Immune responses to implants—a review of the implications for the design of immunomodulatory biomaterials. Biomaterials 2011; 32:6692-709; PMID:21715002; http://dx.doi.org/10.1016/j.biomaterials.2011.05.078
95. Rammelt S, Lang A, Averbeck M, Hofbauer LC, Mai R, Hempel U. A novel method of monitoring the early stages of bone healing. Regen Med 2009; 4(Suppl. 2):S130-1.
96. Förster Y, Gao W, Betz V, Zwipp H, Kalkhof S, von Bergen M, et al. Microdialysis as a method to describe the molecular events in the early phase of bone healing. Biomaterialien 2010; 11:177.